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(71) Applicant
Centre De Recherches Biologiques Virbac (France), Zone Industrielle, Secteur Bleu 47, 06516 Carros Industrie, France

(72) Inventors
Pierre Richard Dick,
Jacques Alexandre Cuvelier

(74) Agent and/or Address for Service
Mathys & Squire, 10 Fleet Street, London EC4Y 1AY

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(58) Field of search
A5B
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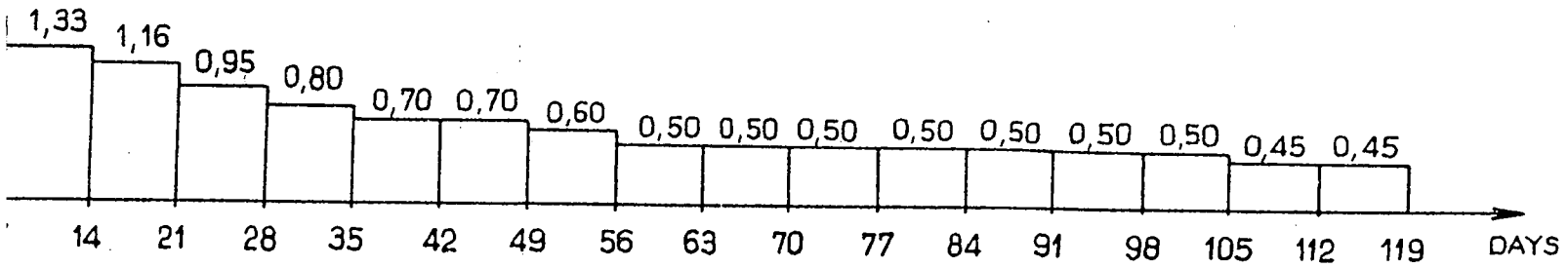
(54) Sustained release devices

(57) Sustained release devices have an insoluble polymer and glycerol ester matrix containing an active substance. Preferred devices are solid implants for subcutaneous administration, containing one or more anabolic substances incorporated in the matrix. The implants give sustained release of the anabolic substance especially in farm animals. The anabolic substance is e.g. estradiol, testosterone, progesterone, nandrolone, trembolone etc. The insoluble polymer may be polypropylene, polyethylene, pvc, polystyrene etc, and the ester can be glycerol palmitostearate, stearate or behenate.

GB 2 167 66

EASED QUANTITIES OF
STRADIOL (µg/ml)

FIG_1



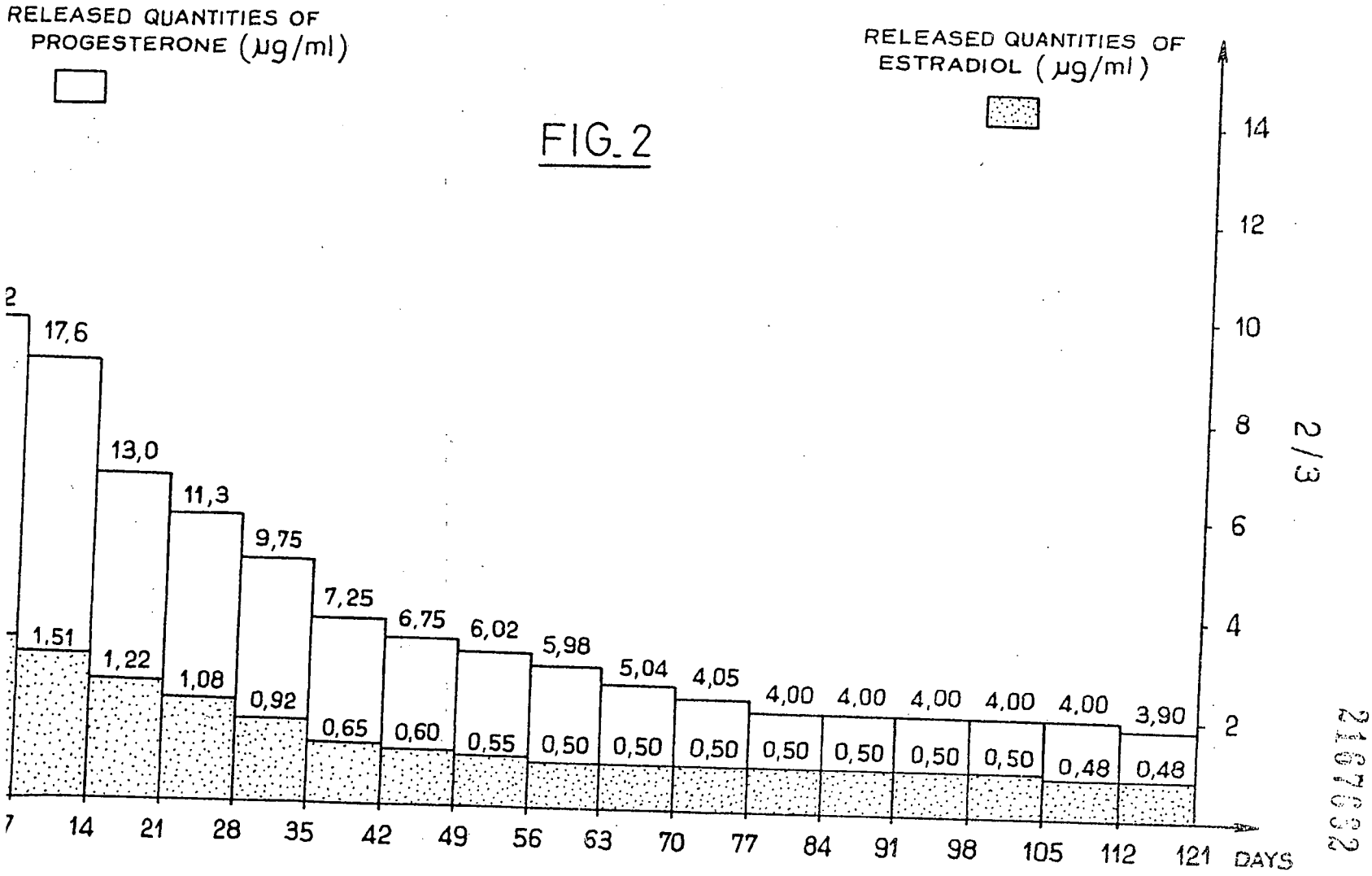


FIG_2

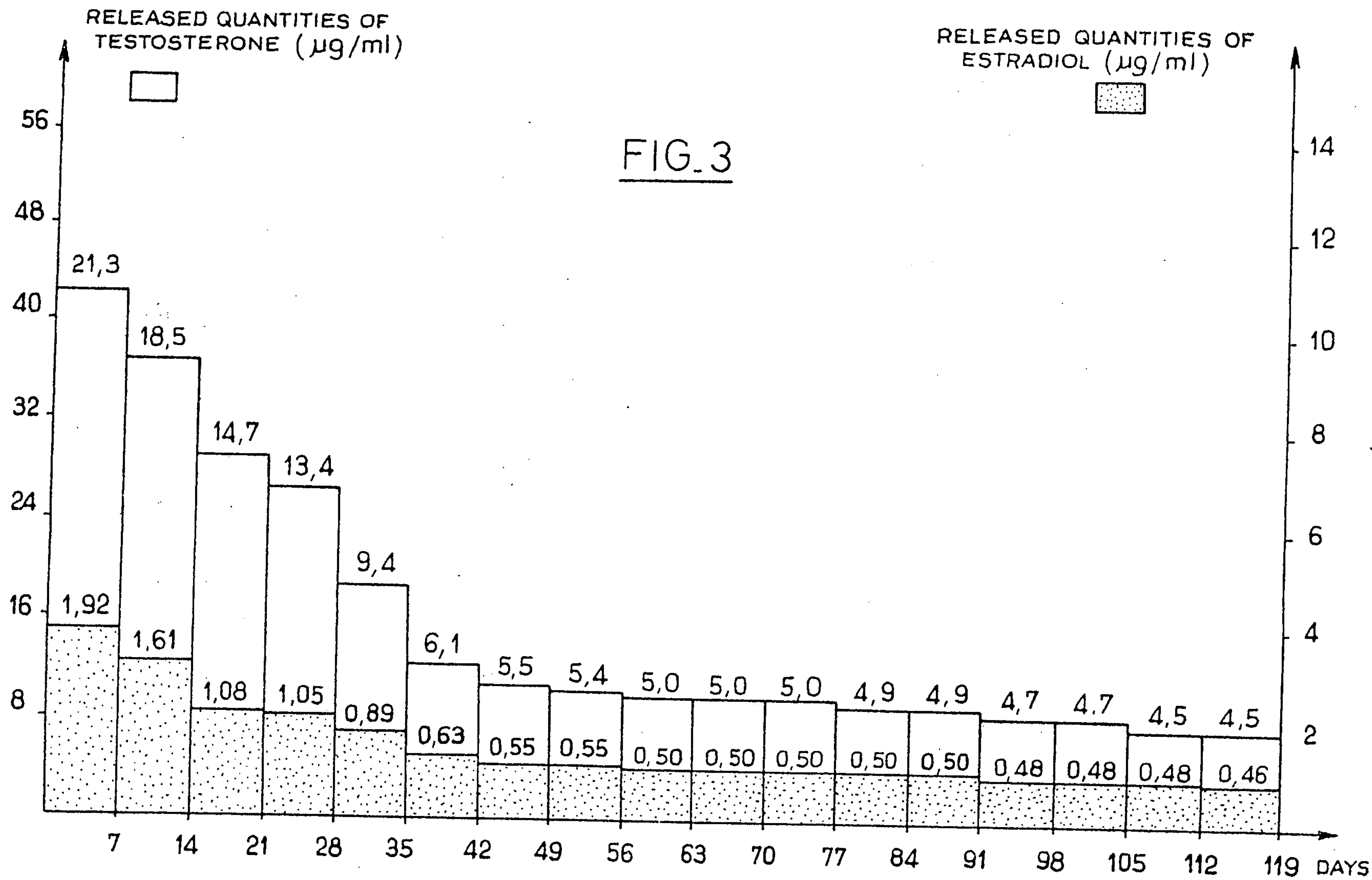

RELEASED QUANTITIES OF TESTOSTERONE (µg/ml)
RELEASED QUANTITIES OF ESTRADIOL (µg/ml)
56
48
40
32
24
16
8
14
12
10
8
6
4
2
21,3
18,5
14,7
13,4
9,4
6,1
5,5
5,4
5,0
5,0
5,0
4,9
4,9
4,7
4,7
4,5
4,5
1,92
1,61
1,08
1,05
0,89
0,63
0,55
0,55
0,50
0,50
0,50
0,50
0,50
0,48
0,48
0,48
0,46
7
14
21
28
35
42
49
56
63
70
77
84
91
98
105
112
119
DAYS

FIG_3

SPECIFICATION

Sustained-release anabolic implants

The present invention relates to cylindrical solid matrices which can be used as subcutaneous implants, wherein the active principle or principles are anabolic agents and wherein the solid matrix consists inter alia of an insoluble polymer. Under the manufacturing and use conditions described in this invention, these matrices behave like sustained-release devices and permit regulated diffusion of the active principle or principles.

In accordance with the present invention, these hormone matrix implants are produced for use as a hormone growth factor in farm animals and in particular in young cattle.

The subcutaneous implantation of anabolic substances (estrogens, androgens or progestrogens) in cattle makes it possible to stimulate the nitrogen retention and its conversion to protein. One consequence of this is an improvement in the degrees of conversion of the nitrogen in the feed to nitrogen in the form of edible proteins. This results in a brisk gain in weight and a more rapid growth of the skeletal muscles and of the tissues other than the sexual organs with the aim of making a profit from livestock production by obtaining higher consumption indices.

The conventional subcutaneous implantation of anabolic substances is effected by means of small tablets of spherical or cylindrical shape, usually called "implants" or "pellets".

These implants are obtained using the method widely known by those skilled in the art, and involve the usual compression techniques. In addition to the active principle or principles present in the composition of these implants, various adjuvants, such as binders, lubricants, disintegrating agents and bulking agents, are incorporated during the manufacturing process.

These implants are considered to be conventional quick-release forms. Although widely used, these forms lead to a quick release of the active principle or principles after subcutaneous implantation in the animal, resulting in a substantial but short-term increase in the hormone level in the organism.

Under these conditions, the anabolic effect is greatly reduced and it therefore becomes essential to repeat the implantations at very short intervals of time. Apart from the technical disadvantages of using this kind of quick-release implant, these very frequent administrations lead to high hormone levels which can, on occasions, be found in the meat of the slaughtered animals. These high hormone residues can sometimes be the cause of physiological disorders in humans who consume this type of meat.

It is for this reason that the implants of the type claimed in the present invention are produced from hydrophobic polymer matrices forming sustained-release devices. These implants ensure a regular distribution of the active principle or principles in the organism so as to maintain their concentration for a given time and at a therapeutically effective level.

Under these conditions, and by varying the ratios between excipients, constant levels of hormone substances which are sufficient to allow the anabolic action but nevertheless close to the physiological levels, so as to avoid high concentration of residues capable of being injurious to public health, can be maintained for several weeks or even several months.

The literature describes sustained-release systems containing anabolic substances whose matrix support consists of silicone-type polymers (European Patent 9 410 filed by Eli Lilly and Company). However, this type of implant calls for a special technology for molding silicone polymerizable in the cold by the use of chemical catalysts.

Other soluble matrix systems, based on polyvinylpyrrolidone or polyvinyl alcohol, are described in U.S. Patent 4 321 252 filed by KEY Pharmaceuticals Inc. These matrices based on estrogenic substances are used by intrauterine administration and are totally soluble in the biological fluids.

The implants described in the present invention are obtained from a hydrophobic polymer matrix and are therefore totally insoluble in water or the biological fluids. In addition to their ability to deliver constant and regular doses of active principles, they are preserved intact in their shape throughout the implantation process. This property therefore makes it possible efficiently to monitor the implantation technique and to facilitate recognition of the implanted animals when they are slaughtered.

Furthermore, the implants according to the present invention are obtained by very conventional methods used in the pharmaceutical industry. The so-called direct compression technique enables the sustained-release implants to be obtained very easily.

The anabolic implants according to the invention consists of an insoluble polymer matrix based on an insoluble polymer associated with a glycerol ester.

To permit compressibility, manufacturing adjuvants, such as talc, dicalcium phosphate etc., are added to the composition.

Within the scope of the invention, the following can be selected from among the active principle or principles having an anabolic action: 17β-estradiol, testosterone, progesterone, nandrolone, trembolone

Within the scope of the present invention, the following were selected among the substances making up the insoluble polymer matrix: insoluble polymers such as polypropylene, polyethylene, polyvinyl chloride, ethylvinyl acetate, polystyrene and polymethacrylate, as well as glycerol esters of the glycerol palmitostearate, glycerol stearate and glycerol behenate type.

Within the scope of the compositions of the invention, it is apparent that the percentage of the insoluble polymer matrix can be between 10 and 60% but more particularly between 15 and 40%, the remaining part being composed of the active principle or principles in a sufficient quantity to give the desired therapeutic effect, and of bulking agents and compression aids.

The insoluble polymer matrix can be produced from a mixture of insoluble polymer and glycerol ester which can vary within the proportions of 1 to 10. Nevertheless, it is apparent from the experiments performed that the best results are obtained for identical quantities of each of the components.

As indicated previously, the sustained-release anabolic implants are obtained by conventional compression methods. In fact, the methods of direct compression on a reciprocating or rotary machine, or of wet granulation, both produce the desired pharmaceutical forms.

The implants produced according to the invention permit the sustained release of the active principle or principles over a period of several weeks.

This property can be checked initially by in vitro diffusion tests, but also by in vivo tests.

The best in vitro test consists in immersing a number of implants, generally corresponding to a therapeutic dose, in a given volume of water and in making a quantitative measurement of the active principle which has solubilized at given intervals of time. In addition, to avoid any saturation phenomenon associated with the low solubility of the active principles, the solvent is totally renewed after each analysis.

This type of test gives results which can be represented in the form of a histogram showing the quantities of active principle released per unit time.

As regards the in vivo tests, a simple method consists in effecting the subcutaneous implantation of one or more pellets in a laboratory animal (rat, guinea-pig or rabbit), then removing the pellets at given times and analyzing the remaining active principle.

Furthermore, as the sustained-release anabolic implants have a direct application in veterinary medicine as growth factors, controlled clinical trials are carried out and show an increase in the weight gain relative to groups of control animals.

The present invention is illustrated by the series of examples which follow, but these do not reduce its scope.

Composition examples

Example 1

Implants having the percentage composition indicated below are produced by the direct compression technique:

17β-Estradiol	5.7%
Talc	2%
Polyvinyl chloride (PEVIKON PE 737 P)®	10%
Glycerol palmitostearate (PRECIROL ATO - 5)®	10%
Dicalcium phosphate (ENCOMPRESS)®	72.5%

The implants obtained are cylindrical in shape and have a unit weight of 35 mg. They contain 2 mg of 17β-estradiol and their hardness, measured on a FLISSA automatic machine, is 10.2 KN.

Example 2

Implants having the percentage composition below are produced by the direct compression technique:

17β-Estradiol	5.7%
Talc	2%
Microporous polypropylene (ACCUREL KPP)®	20%
Glycerol stearate (PRECIROL WL 2 155)	10%
Dicalcium phosphate (ENCOMPRESS)®	62.3%

The implants obtained have the same shape, weight and hardness characteristics as those obtained in Example 1.

Example 3

Cylindrical implants having the following percentage composition are produced by the wet granulation method:

17β-Estradiol 5.7%
Progesterone 57%
Talc 3%
Microporous polypropylene (ACCUREL KPP) ® 10%
Glycerol stearate (PRECIROL WL 2 155) ® 10%
Dicalcium phosphate (ENCOMPRESS) ® 14.3%

The implants obtained contain a 2 mg dose of estradiol and a 20 mg dose of progesterone. They weigh 35 mg and their hardness is 9.5 KN.

Example 4

Spherical implants having the following percentage composition are produced by the direct compression technique:

Zeranol 30%
Talc 2%
Magnesium stearate 1%
Microporous polyethylene (ACCUREL HDPE) ® 15%
Glycerol behenate (COMPRITOL 888) ® 15%
Dicalcium phosphate (ENCOMPRESS) ® 37%

The implants obtained contain 12 mg of zeranol and have an individual weight of 40 mg.

Example 5

Cylindrical implants having the following percentage composition are produced by compression, using the wet granulation method:

17β-Estradiol 5.7%
Testosterone 57%
Talc 2%
Magnesium stearate 1%
Microporous polypropylene (ACCUREL KPP) ® 10%
Glycerol stearate (PRECIROL WL 2 155) ® 10%
Dicalcium phosphate (ENCOMPRESS) ® 14.3%

These implants, which have a unit weight of 35 mg and a hardness of 10.5 KN, contain 2 mg of estradiol and 20 mg of testosterone.

Example 6

Cylindrical implants having the following percentage composition are produced by compression, using the wet granulation method:

17β-Estradiol benzoate 5.7%
Trembolone acetate 57%
Talc 2%
Magnesium stearate 1%
Polyvinyl chloride (PEVIKON PE 737) ® 15%
Glycerol palmitostearate (PRECIROL ATO-5) ® 5%
Dicalcium phosphate (ENCOMPRESS) ® 14.3%

Example 7

A spherical implant having the following percentage composition is produced by direct compression:

17β-Estradiol benzoate	6.25%
Talc	2%
Magnesium stearate	1%
Polymethacrylate (EUDRAGIT RS) ®	10%
Glyceroi behenate (COMPRITOL 888) ®	5%
Dicalcium phosphate (ENCOMPRESS 278) ®	75.75%

These implants weigh 40 mg and contain 2.5 mg of estradiol benzoate.

In vitro diffusion tests

Example 8

The in vitro diffusion test is carried out on the implants whose composition is indicated in Example 1 (2 mg of estradiol per implant). The test is performed in the following manner: 10 implants F_1 are immersed in 500 ml of a physiological serum/ethanol mixture (90/10). The hermetically sealed container is placed in an enclosure at 37°C. A sample of solvent is taken every 7 days and the whole of the liquid is replaced by the same volume of fresh mixture.

The operation is carried out for about 120 days.

The quantity of 17β-estradiol contained in each sample taken is determined by the method of high performance liquid chromatography. The experimental conditions (stationary phase: hypersil C18 5 μ, eluent: acetonitrile/water 60/40, detection: UV at 280 nm) make it possible to obtain a correct plot of the chromatogram. The quantity present in the sample can be read off directly by coupling the detector with a computer integrator.

The results are presented in the form of a histogram (see plate 1/3), which shows the quantities of estradiol, expressed in μg per ml of medium, on the ordinate and the 7-day intervals on the abscissa. The figures in each column correspond to the total quantity of estradiol released in mg per 7-day period.

The general shape of the histogram shows that the "in vitro" behaviour of the implant F_1 is that of a sustained-release system. After high values, the system equilibrates to give mean values of the order of 0.5 mg for 7 days. Over 120 days, it is found that the total quantity of estradiol released is 12.16 mg, i.e. 60.80% of the total initial dose.

Example 9

The same test as described above is carried out, but this time on the implants whose composition is indicated in Example 3 (2 mg of estradiol and 20 mg of progesterone). The experimental protocol and conditions are identical in every respect to those of the previous test.

The results obtained for estradiol and for progesterone are collated in the form of a histogram on plate 2/3. The respective quantities of estradiol and progesterone, in μg per ml of medium, are plotted on 2 different scales on the ordinate. Over 120 days, the total quantities released are respectively 129.84 mg, i.e. 64.92%, for progesterone and 12.18 mg, i.e. 60.95%, for estradiol.

Example 10

The same test as described above is carried out, but this time on the implants whose composition is indicated in Example 5 (2 mg of estradiol and 20 mg of testosterone).

The experimental protocol and conditions are identical in every respect to those of the previous test.

The results obtained for estradiol and for testosterone are collated in the form of a histogram on plate 3/3.

Over 120 days, the total quantities released are respectively 137.5 mg, i.e. 68.75%, for testosterone and 12.68 mg, i.e. 63.40%, for estradiol.

In vivo diffusion tests

Example 11

5 implants whose composition is indicated in Example 3 are placed under the skin of 10 selected albino rabbits, under anesthetic.

Every 20 days, the implants are removed from 2 animals under anesthetic. Quantitative analysis of the remaining concentration of 17β-estradiol and progesterone is carried out by high performance liquid chromatography. The results obtained are collated in Table I and the values in mg of active substance per implant are the means of 10 implants. These results show practically linear elimination kinetics.

TABLE I

Days	0	20	40	60	80	100
Estradiol mg	2.05	1.51	1.13	0.81	0.41	0.09
Progesterone mg	20.2	16.1	11.9	8.7	4.3	1.1

Example 12

This test is carried out under the same conditions as the test described in Example 11, but using the implants whose composition is indicated in Example 5. The results are indicated in Table II and show a similarity to those of the previous example.

TABLE II

Days	0	20	40	60	80	100
Estradiol mg	2.01	1.47	1.09	0.78	0.39	0.05
Testosterone mg	20.3	16.5	12.1	8.1	4.0	0.9

Clinical trials

Example 13

The clinical trial consists in checking the anabolic action of the implants on young calves for slaughter by evaluating the increase in the mean daily weight gain (MDG). The test is carried out on the implants whose composition is described in Example 3. The single dose administered corresponds to 10 implants, i.e. to 20 mg of 17β-estradiol and 200 mg of progesterone per animal. The implantation is effected subcutaneously in the dewlap.

The implanted calves are 10 days old, of male sex and of the FFPN dairy breed. The 30 animals treated are weighed individually and the mean live weight (MLW) is compared with that of 30 identical animals making up the control group.

The experiment is conducted over 90 days, the animals being placed under identical rearing conditions.

The table which follows (Table III) collates the values of the mean live weight at given intervals of time and the value of the MDG in grams, calculated using the formula:

$$MDG_{D1} = \frac{MLW_{D1} - MLW_{D0}}{D_1 - D_0}$$

The results show a clearly significant weight gain and the weight curve of the animals is characterized by a linear and constant change. Moreover, it is noted that the anabolic effect sets in at a very early stage of the animals' growth.

The weight gain is about 11% relative to the control group.

TABLE III

		Control group	Treated group
DO	MLW (kg)	46.8	46.5
	MDG (g)	-	-
D24	MLW (kg)	61.1	61.7
	MDG (g)	596	633
D47	MLW (kg)	88.8	94.3
	MDG (g)	894	1017
D69	MLW (kg)	115.5	124.9
	MDG (g)	996	1136
D85	MLW (kg)	132.4	146.9
	MDG (g)	1007	1181

Example 14

A clinical trial is carried out under the same conditions as those described in Example 13.

The animals are female calves for slaughter of the FFPN dairy breed. The implants used are those described in Example 6. 10 implants are administered per animal, i.e. 20 mg of 17β-estradiol and 200 mg of testosterone.

The results collated in Table IV also show a significant weight gain (10.5%) relative to the control

TABLE IV

		Control group	Treated group
DO	MLW (kg)	46.4	46.3
	MDG (g)	-	-
D24	MLW (kg)	59.3	61.0
	MDG (g)	538	613
D47	MLW (kg)	85.9	93.3
	MDG (g)	840	1000
D69	MLW (kg)	113.7	123.5
	MDG (g)	975	1119
D85	MLW (kg)	130.5	144.2
	MDG (g)	989	1152

CLAIMS

1. A sustained-release device which consists of a solid matrix based on hydrophobic insoluble polymers associated with glycerol esters, so-called bulking substances and one or more active substances.

2. A sustained-release device as claimed in claim 1, wherein the active substance or substances are anabolic agents (estrogens, androgens or progestogens) which can represent from 5 to 60% by weight of the composition.

3. A sustained-release device as claimed in claim 1, wherein the solid matrix is baded on insoluble polymers such as polypropylene, polyethylene, polyvinyl chloride, polystyrene, polymethacrylate and ethylvinyl acetate, associated with glycerol esters, which can together represent from 10 to 50% by weight of the composition.

4. A device as claimed in claim 1, produced for administration by subcutaneous implantation in animals and more especially cattle and sheep, and defined as a sustained-release anabolic implant.

5. A sustained-release anabolic implant as claimed in claims 2 to 4, characterized by its growth factor property whose physiological action lasts between 50 and 200 days.

6. A sustained-release anabolic implant as claimed in claims 2 to 4, manufactured industrially by the compression technique.

7. A sustained-release anabolic implant as claimed in claims 2 to 4, wherein the active substances are taken from the group comprising: 17β-estradiol or its esters, progesterone or its esters, testosterone or its esters, nandrolone, trembolone or its esters and zeranol.

8. A sustained-release anabolic implant as claimed in claim 7, which consists of the anabolic substance 17β-estradiol, an insoluble matrix based on polypropylene and glycerol stearate, and bulking agents enabling it to be manufactured industrially by direct compression.

9. A sustained-release anabolic implant which consists of a mixture of the anabolic substances 17β-estradiol and testosterone, an insoluble matrix based on polypropylene and glycerol stearate, and bulking agents enabling it to be manufactured industrially by compression.

10. A sustained-release anabolic implant which consists of a mixture of the anabolic substances 17β-estradiol and progesterone, an insoluble matrix based on polypropylene and glycerol stearate, and bulking agents enabling it to be manufactured industrially by compression.

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